BLOOD PRODUCTS ADVISORY COMMITTEE
104th Meeting, September 20, 2012
FDA Fishers Lane Building
5630 Fishers Lane, Room 1066
Rockville, MD

ISSUE SUMMARY

Topic II: Safety and Efficacy of OctaplasLG, Solvent/Detergent, Ligand Gel Affinity Chromatography Treated Plasma

Issue: FDA seeks the advice of the Committee on whether or not the data show that OctaplasLG has an acceptable safety profile and is effective in the patient populations for which indications are being sought.

Background:

OctaplasLG (ligand gel) is a solvent/detergent (S/D) treated, blood group specific, pooled human plasma product developed by Octapharma. OctaplasLG has been marketed since 2009 and the previous versions have been marketed since 1992, in several European countries and Australia (Table 1). Octapharma is currently seeking licensure for OctaplasLG in the US.

OctaplasLG (Generation 2b) differs from previous generations of the product, Octaplas® lyophilized (Generation 1) or Octaplas® frozen (Generation 2a), in the following ways:

- the time of S/D treatment at 30 $\pm$ 1°C in the manufacture of OctaplasLG has been reduced from 4-4.5 hours to 1-1.5 hours to improve the concentration of S/D labile plasma proteins such as plasmin inhibitor (PI, also known as α_2-antiplasmin) and Protein S (PS).
- the manufacturing process includes a chromatographic step for the selective binding of prions (PrP^{Sc}) to a ligand in an attempt to reduce the risk of vCJD

Octapharma has also developed Uniplas/UniplasLG, a non-blood group specific, solvent detergent plasma. Uniplas/UniplasLG differs from Octaplas/OctaplasLG only in that anti-A and anti-B antibodies are removed; thereby, making it universally transfusable. Uniplas/UniplasLG is not licensed in the US or EU.

Information on Octaplas® lyophilized (Generation 1) or Octaplas® frozen (Generation 2a) and Uniplas/UniplasLG is presented herein (Table 1) since these products are included in some of the clinical trials submitted in support of the safety and efficacy of OctaplasLG.

Table 1: Generations of Solvent Detergent Plasma (SDP*) Products Produced by Octapharma

Generation**	Product Name	S/D Treated	Product Formulation	Blood Group Specific	Ligand Gel Chroma-tography	Current availability status
1	Octaplas®	yes	lyophilized	Yes	No	No
2a	Octaplas®	yes	liquid, Frozen	Yes	No	Yes, since 1992 in EU
2b	OctaplasLG	yes	liquid, frozen	Yes	Yes	Yes since 2009 in EU
3a	Uniplas	yes	liquid, frozen	No	No	No
3b	UniplasLG	yes	liquid, frozen	No	Yes	No

***** SDP will be used to refer to all Generations of the Octapharma solvent/detergent treated plasma product.

**For all generations, the time until a plasma donation is frozen (core temperature -25°C) is 8 to 24 hours for recovered plasma and 18 hours (freezing process has to start after 6h at the latest) for Source Plasma. Octapharma does not differentiate between 8 hours and 24 hours plasma in their warehouse.

Octapharma has submitted data to support the following two of the six indications carried by FFP and PF24 which are listed in the current AABB Circular of Information and currently licensed in the US.

- "Management of preoperative or bleeding patients who require replacement of multiple coagulation factors
- Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura - TTP)"

For reference, the other four indications for FFP and PF24 are:

- "Patients undergoing massive transfusion who have clinically significant coagulation deficiencies;
- Patients taking warfarin who are bleeding or need to undergo an invasive procedure before vitamin K could reverse the warfarin effect or who need only transient reversal of warfarin effect;
- Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available;
- Management of patients with rare specific plasma protein deficiencies, such as C1 inhibitor, when recombinant products are unavailable."

Data Sources Reviewed

FDA reviewed a total of 17 studies submitted by Octapharma in support of the OctaplasLG product approval for the proposed indications. Most of these studies were uncontrolled and/or underpowered, and were not hypothesis driven. One of the studies was a retrospective study that evaluated tolerability. In this study ~ 5000 units of Octaplas® were transfused to 950 subjects and no AEs were reported. Since it is unlikely that there would be no AEs given the size of this study, FDA has excluded this study from the overview of the data presented in this Issue Summary. Five of the remaining 16 studies were literature reports without complete study reports and so were considered by FDA only for safety evaluation of the product. FDA has considered the remaining 11 clinical studies from the entire dataset submitted by Octapharma in support of safety and efficacy of OctaplasLG and are discussed in this issue summary.

Three of the 11 studies include FFP as the comparator product (LAS-1-02-D, 19/PLAS/IV/91 and LAS-1-03-UK). Four of the 11 studies are bridging studies that compare one generation of the product with another (LAS-201, LAS-203, UNI-110, UNI-101). In addition, FDA has reviewed submitted pharmacovigilance data on all generations of Octapharma pooled plasma products dating back to the first approval in 1992 of Octaplas® in the EU. Finally, FDA has considered published literature relevant to the safety and effectiveness of OctaplasLG.

Product:

OctaplasLG is prepared from 630 to 1,520 single-donor plasma units of the same blood group, collected in US FDA licensed plasma donation centers. The units are frozen at the time of collection, and thawed at the Octapharma manufacturing facility. Whole cells and cell fragments/debris are removed by 1.0 μm filtration. Subsequently, the plasma pool is treated for 1-1.5 hours at 30 ±1°C with a combination of solvent [1% Tri(n-butyl) phosphate (TNBP)] and detergent (1% Octoxynol-9) to inactivate enveloped viruses. These S/D reagents are later removed by oil and solid phase extraction. Thereafter, the product solution is passed through an affinity ligand column intended to remove prion protein. After sterile filtration, OctaplasLG is filled in 200 mL aliquots into plasma bags and frozen to a core temperature of ≤ -65°C, then stored at ≤ -18 °C.

All plasma donations are tested for viral markers in compliance with requirements of FDA. Only plasma pools that are negative by serological tests and/or nucleic acid amplification technique (NAT) assays for HIV, HBV, HCV and HAV, and that contain no more than 10.0 IU/μL Parvovirus B19 DNA are accepted for manufacture of OctaplasLG. Additional safety of OctaplasLG is based on S/D treatment, which is primarily effective in the inactivation of enveloped viruses. The safety of the product with respect to HAV and Parvovirus B19, two non-enveloped viruses, is enhanced by setting a minimum specification for the level of neutralizing HAV and Parvovirus B19 antibodies in the product. The mean cumulative virus reduction factor for each virus or for a model virus that is representative of the target pathogen is summarized in Table 2.

Table 2: Viral Reduction Capacity of OctaplasLG achieved by SD treatment

Production Step	HIV-1	PRV	SBV	BVDV	WNV	VACV
S/D treatment [log_{10}]	≥ 6.18	≥ 5.03	≥ 5.31	≥ 5.12	≥ 5.63	≥ 5.00

HIV-1: Human Immunodeficiency Virus–1
PRV: Pseudorabies Virus (model for HBV)
SBV: Sindbis Virus (model for HCV)
BVDV: Bovine Viral Diarrhea Virus (model virus for HCV)
VACV: Vaccinia Virus
WNV: West-Nile Virus

The safety of OctaplasLG regarding HEV, a non-enveloped virus, is dependent on both the specific IgG antibody level and the initial HEV load in the manufacturing plasma pool. FDA has requested that the manufacturer implement a HEV NAT in order to limit the viral load in the manufacturing pool as negative for HEV RNA with a NAT assay that has a limit of detection of 2.5log_{10} copies/mL or less. The presence of anti-HEV antibody in the manufacturing pool may also contribute to the neutralization of the virus. However, levels of anti-HEV that are protective have not been determined, so the manufacturer has not been asked to establish a specification with respect to anti-HEV antibodies.

In order to reduce the risk of vCJD transmission, Octapharma has introduced into the manufacturing process, an affinity chromatography step designed to remove prion protein. The affinity ligand (LG) was selected based on its ability to capture the PrP^{Sc} prion protein while maintaining plasma quality. Prion clearance studies were performed with the 263K strain of hamster-adapted scrapie. Clearance data indicated, however, that the prion infectivity removal capacity of the LG chromatography step was limited to a reduction factor of 0.83 log_{10}.

Octaplas®and OctaplasLG were characterized for relevant coagulation factors, anticoagulant proteins, protease inhibitors, and procoagulant activity as compared to FFP and reference values (Table 3).

Table 3: Biochemical profile of OctaplasLG, Octaplas® G-2a and FFP expressed as mean and range of values

Parameter	Reference* (n=100)	OctaplasLG (n=12)**	Octaplas® G-2a (n=24)	FFP (n=12)
aPTT (s)	28-41	29.5 (28.0-31.0)	33.4 (27.2-41.7)	35.2 (31.7-42.5)
FV (IU/ml)	0.54-1.45	0.85 (0.70-1.00)	0.95 (0.70-1.10)	0.90 (0.73-1.50)
FVII (IU/ml)	0.62-1.65	1.00 (0.70-1.20)	1.02 (0.89-1.40)	0.95 (0.67-1.38)
FVIII (IU/ml)	0.45-1.68	0.89 (0.70-1.30)	0.78 (0.50-1.00)	0.76 (0.52-1.13)
FX (IU/ml)	0.68-1.48	0.93 (0.85-1.03)	0.86 (0.76-0.92)	0.79 (0.62-0.99)
PC (IU/ml)	0.58-1.64	0.98 (0.90-1.10)	0.90 (0.75-1.06)	0.89 (0.79-1.05)
PS (IU/ml)	0.56-1.68	0.61 (0.50-0.70)	0.50 (0.41-0.55)	1.03 (0.71-1.39)
PI (IU/ml)	0.72-1.32	0.48 (0.30-0.50)	0.32 (0.26-0.40)	1.04 (0.95-1.18)

*Based on the testing of 100 healthy blood donors and defined by the 2.5 and 97.5 percentiles

** Summary of biochemical profile from 12 conformance lots made from US Source/recovered plasma submitted in the BLA

As shown in Table 3, activities for relevant plasma proteins are comparable between Octaplas®, OctaplasLG and FFP except for PS and PI. PS levels in OctaplasLG are within the lower limits of the Reference range, whereas PI levels are below the lower limits of the Reference and the FFP ranges. PS and PI are further decreased in Octaplas®.

FDA Analysis of Clinical data:

The sponsor submitted clinical studies involving all generations of SDP: Octaplas® (generation 1), Octaplas® (generation 2a), OctaplasLG (generation 2b), Uniplas (generation 3a) and UniplasLG (generation 3b). Data from prior generation products were submitted by the manufacturer due to the similarities in manufacturing and biochemical properties between the OctaplasLG and prior generation products. Data from 16 studies (11 with complete study reports and 5 from the literature), including a total of 585 patients who received SDP were submitted in support of efficacy and safety (Table 4 and Appendix 1). Of the 11 clinical studies with complete reports, 2 were safety studies; therefore, a total of 9 studies were considered by FDA for efficacy evaluation of the product. All studies and available pharmacovigilance data were considered in FDA's evaluation of safety.

Table 4 summarizes the studies and reports according to type and Table 5 summarizes the clinical setting and numbers of subjects administered SDP

Table 4: Studies to Support Safety and Efficacy

Study	Design	Product(s)	Disease	Total Subjects
1. Studies using FFP as a comparator				
LAS-1-02-D 1998	Prospective, controlled, open-label	Octaplas (G-2a*) and FFP	Open heart surgery	67
19/PLAS/IV/91 1992	Prospective, open-label, parallel group	Octaplas (G-1**), no plasma, and FFP	Open heart surgery	66
LAS-1-03-UK 1995	Prospective, randomized, multi-center, open-label	Octaplas (G-2a) and FFP	Liver disease, liver transplantation, TTP	55
2. Bridging studies				
LAS-203 2009	Phase 1, prospective, randomized, open-label, controlled, cross-over, single center	Octaplas (G-2a) and OctaplasLG	Healthy volunteers	60
UNI-101 1999	Phase II, prospective, randomized,	Octaplas (G-2a) and Uniplas	Elective open heart surgery	84

	controlled, blinded			
LAS-201 2008	Observational, prospective, multi-center, sequential cohort, open-label	Octaplas (G-2a) and OctaplasLG	any clinical condition with a need for plasma	125
UNI-110 2009	Phase 1, prospective, randomized, double-blind, controlled, cross-over, single center	OctaplasLG and UniplasLG	Healthy volunteers	30
3. Single arm studies				
3PLASIV90 1990	Prospective, open-label	Octaplas (G-1)	Hereditary or acquired coagulation factor deficiency	11
LAS-Study 1-D 1992	Prospective, open-label, single center	Octaplas (G-1)	ICU patients w/ disseminated intravascular coagulation (DIC)	30
4. Safety Studies				
PVI/ 003 1997	Prospective, open labeled	Octaplas (G-2a)	Rh D negative patients requiring plasma therapy	5
PVI/B004 1997	Prospective, open labeled	Octaplas (G-2a)	Plasma given as per clinical need	20
5. Literature reports				
Chekrizova et al. 2006	Retrospective	Uniplas and Octaplas (G-2a)	Neonates with coagulopathy; Ob/Gyn patients; liver disease	111
Scully et al. 2007	Retrospective	Octaplas (G-2a) and cryosupernatant	Acute TTP	32
Edel et al. 2010	Retrospective	Octaplas (G-2a)	Acute TTP	8
Santagostino et al. 2006	Phase 4, prospective, open-label, multi-center	Octaplas (G-2a)	Inherited coagulation disorders	17
Demeyere et al. 2010	Prospective, randomized, single	Octaplas (G-2a) and prothrombin	Cardio-pulmonary	40

	center	complex concentrates	bypass surgery	
6. Postmarketing Pharmacovigilance Reports				
Octaplas G-2a PSUR reports October 1989-August 2011	N/A	N/A	N/A	
Octaplas LG PSUR reports June 2009-August 2011	N/A	N/A	N/A	

*Generation 2a **Generation 1

Table 5: Clinical Setting and Numbers of Subjects Administered SDP*

Clinical Settings	Number of Subjects
Inherited or acquired single or combined coagulation factor deficiencies	96 (41 neonates 24 – 43 weeks; 28 premature)
Cardiac/Thoracic Surgery	118
Liver Disease	45 (15 pediatric subjects age 12 days – 16 years)
Liver Transplant	16
Thrombotic Thrombocytopenia Purpura (TTP)	48
Disseminated Intravascular Coagulation	63
Reversal of oral anticoagulation (subjects undergoing semi-urgent cardiac surgery)	20
Ob/Gyn Emergencies (hemorrhagic)	38 (26 Ob/12 Gyn)
Plasma exchange not for TTP	27
Non-cardiothoracic peri/intra-operative use (e.g., ortho, neuro)	18
Non-surgical bleeding (e.g., GI)	4
Other (anemia, oral anticoagulation)	2
Healthy volunteers	90
TOTAL	**585**

*Based upon FDA's evaluation and tabulation of the data from 9 studies with complete study reports and 5 literature reports.

Section 1: Studies using FFP as a comparator

Study LAS-1-02-D: (Octaplas® G-2a in patients with coagulopathy, N=67)

The study was designed as a prospective, single center, non-randomized, open-label, study. Subjects at risk for hemorrhage due to acquired coagulopathy (blood loss, dilution or DIC) were enrolled.

The objectives of this study were to evaluate safety and efficacy of Octaplas® (G-2a) compared to FFP in subjects in the intensive care unit after open heart surgery. The safety outcome measures included laboratory assessment of activation of the blood coagulation/fibrinolysis system (prothrombin fragments 1+2, fibrin split products, plasmin-antiplasmin complex, D-Dimer), thrombotic complications and changes in vital signs (heart rate, blood pressure and body temperature) after treatment.

The efficacy outcome measures included coagulation parameters: platelets, PT, aPTT, fibrinogen and FVIII, coagulation inhibitors: antithrombin (AT), PS, free PS, PI and trypsin inhibitor (TI) and the investigator's subjective assessment of "general impression" of the hemostatic effect.

The study consisted of 67 patients (36 Octaplas®, 31 FFP). The mean PS activity levels at 30 and 60 minutes after transfusion were comparable in the two groups and were also not different from baseline in each group. As expected (see Table 3 above), PI levels were lower for the Octaplas® group when compared to FFP. The remaining laboratory parameter values were similar in the two groups.

The investigators concluded that the overall hemostasis was good or satisfactory in 72% of the Octaplas® group and 77% of the FFP group. The study was underpowered to detect any differences in the efficacy measure.

There were no adverse drug reactions reported, and no thrombotic complications were observed during and after the infusion of the products. 14 patients died during this study, 4 in the Octaplas® treatment group and 10 in the FFP group. In all cases death was judged to be unrelated to the treatment. No differences between the treatment groups with respect to vital signs were observed.

Study19/PLAS/IV/91 (Octaplas®G-1 in patients undergoing open heart surgery, N=66)

The study was designed as an open label, controlled (between the two active groups), non-randomized single center study enrolling three different groups of subjects receiving either Octaplas® G-1 (n=20), FFP (n=20) or no plasma (n=26). The objective of this study was to compare the efficacy and safety of Octaplas® with FFP in subjects

undergoing open heart surgery. The efficacy outcome measures included blood loss, postoperative course, hematology and global coagulation parameters and plasma colloid osmotic pressure. Safety assessment included AEs and viral safety tests at 6 months.

There were no differences between the two active treatment groups in post-operative blood loss, need for surgical revision for bleeding, time on the respirator, circulatory support, hospital stay and coagulation parameters. The Octaplas® group received an average of 3.5 units (range 1-17), and FFP group received an average of 4.05 units (range 2-16).

No serious and/or unexpected AEs occurred, and no patients dropped out of the study for safety reasons. One patient in the Octaplas® group experienced a transient increase in temperature. No abnormal liver function tests and seroconversions were observed in 16 patients who were followed for 6 months after receiving Octaplas®.

Study LAS-1-03-UK (Octaplas® G-2a in patients with liver disease, liver transplantation, and TTP, N=52)

The study was single blind (patients were unaware of the product they received), prospective, and randomized. Of the 52 subjects who completed the study, 24 liver disease (LD) subjects (11 FFP, 13 Octaplas®), 25 liver transplant (LT) subjects (13 FFP, 12 Octaplas®) and 3 TTP subjects were fully evaluable. All TTP subjects received Octaplas®.

The primary objective of this study was to evaluate the efficacy and safety of Octaplas®, compared with FFP, used for the management of the coagulopathy of LD and LT, and in the management of newly diagnosed TTP requiring either plasma infusion or plasma exchange.

The efficacy outcome measures included maintenance of adequate coagulation factors in the three clinical conditions and reversal of pre-existing laboratory abnormalities.

For safety outcomes, AEs within the first 24 hours following infusion, and virology testing before and 6 months after infusion were evaluated.

The outcomes of the study show that Octaplas® was as effective as FFP in correcting coagulopathy associated with LD and LT. All patients in the TTP group attained platelet counts of $> 50 \times 10^9$/L by day 10. There were 2 drug reactions in 1 subject (nausea, pruritis) who received Octaplas®. No thrombotic events were reported.

Section 1: Conclusions

In total, 185 subjects were studied in three trials that compared safety and efficacy of Octaplas® to FFP in clinical conditions associated with coagulopathy. Taken together, data from these studies showed no difference in efficacy or safety outcomes between

prior generation Octaplas® products and FFP in various clinical conditions that require replacement of multiple coagulation factors.

Section 2: Bridging studies

Study UNI-101: (Uniplas, Octaplas® G-2a or no plasma in cardiopulmonary bypass surgery patients, N=84)

The study was single (observer) blinded with three randomized parallel active treatment groups and one no plasma treatment group, in cardiopulmonary bypass surgery.

At hospitalization, eligible patients were stratified into 1 of 3 groups according to their blood group:

- Stratum 1 = A or B
- Stratum 2 = AB
- Stratum 3 = O

Within each stratum, patients who required plasma transfusion were randomized to receive either Uniplas or Octaplas® G-2a. A no-plasma group included all subjects who gave informed consent and who did not require plasma transfusion; therefore, this group represented a different patient population (e.g., required less concomitantly administered blood products and had shorter bypass times) in comparison to the other 3 groups.

To summarize the 4 groups:

- Group 1 = subjects with blood groups A, B or AB receiving Uniplas (n = 25)
- Group 2 = subjects with blood group O receiving Uniplas (n = 11)
- Group 3 = subjects with any blood group receiving Octaplas® G-2a (n = 19)
- Group 4 = eligible subjects who did not require any peri-operative plasma transfusion (no-plasma group) (n = 29)

The primary objective of this study was to compare the safety of Uniplas with Octaplas® G-2a during open heart surgery (valvular, coronary artery bypass or a combination of the two). Assessment of efficacy was a secondary objective and included assessment of global coagulation by measuring aPTT and activated clotting time (ACT) during surgery and in the post-operative period.

Uniplas or Octaplas® was administered in units of 200 mL bags in an amount dependent upon the clinical condition (coagulopathy due to blood loss and/or dilution, and for warfarin reversal). Two to 3 units were administered as a starting regimen for subjects requiring plasma transfusion. Blood samples for laboratory assessment of aPTT and ACT were collected at appropriate time points which included post-operative days one and two.

In total 84 subjects were enrolled and evaluated for safety. Measured values of aPTT and ACT were available for 73 subjects. The laboratory values of aPTT and ACT were

comparable in the three active treatment groups: aPTT values returned to baseline by post-operative day 1 and ACT values were slightly below baseline at the conclusion of surgery.

In total, 55 AEs were recorded during the study period. The AEs were evenly distributed in the 4 groups although no bleeding complications or need for reoperation was reported for the no plasma group. Bleeding and the need for reoperation occurred in 2 of the patients who received Uniplas and 3 of the patients who received Octaplas®. No thrombotic complications were reported. The remainder of the reported AEs (e.g. atrial flutter, decreased cardiac output etc.) appeared to be related to the underlying cardiac condition. FDA agrees with Octapharma's assessment that the reported events were not causally related to either treatment.

Study UNI-110: (OctaplasLG and UniplasLG in healthy volunteers, N=30)

Study UNI-110 had a cross-over design. The primary objective of this study was to compare the safety of UniplasLG and OctaplasLG, and secondarily to compare the two products, with respect to the change in the measured coagulation parameters (aPTT, fibrinogen, FII, FV, FVII, FVIII, FIX, FX, FXI, PS and PI) over time (baseline, immediately following plasmapheresis and after infusion with SDP product). Plasma (600 mL) was intentionally removed from two groups of healthy volunteers at least 18 years old, with blood groups A, B or AB and replaced with either OctaplasLG or UniplasLG (1200 mL). After a 4 week washout period, subjects underwent a second 600 mL plasmapheresis and were replaced with the alternate product, i.e., those individuals who initially received OctaplasLG received UniplasLG and vice versa. Fifteen subjects were in each of the two treatment sequences for a total of 30 subjects.

Mean values of coagulation parameters were within the normal range and variations in their levels were similar between treatment groups.

92 AEs in 27 subjects were reported. The most frequent AEs were paraesthesia, headache and urticaria, and occurred at similar rates in the two treatment arms. Please note that the subjects were not pre-medicated with either anti-allergic or antipyretic medications.

Study LAS-201: (Octaplas® G-2a or OctaplasLG in patients needing plasma for any clinical condition, N=125)

The objective of this study was to assess the efficacy and safety of Octaplas® G-2a compared to OctaplasLG.

This study was designed as a non-interventional, sequential cohort, observational, open-label, prospective, multi-center study. Patients in need of plasma therapy were enrolled. The observation period per patient depended on the indication to be treated, but generally was expected to be a period of 1 to 2 days. Initially, all patients enrolled in the study received Octaplas® and when OctaplasLG was marketed, an additional 60 patients were enrolled.

In total, 65 patients were enrolled into the Octaplas® G-2a cohort and 60 patients were enrolled into the OctaplasLG cohort. The efficacy of the treatment with Octaplas® or OctaplasLG was judged by the investigator based on clinical and laboratory parameters relevant for the indication. However, study subjects were not enrolled until after the study physicians knew whether the treatment was successful and whether any adverse reactions had occurred, leading to potential enrollment bias.

For some patients, more than one treatment episode with Octaplas® or OctaplasLG was administered. Judgment regarding success was decided from the individual's last treatment episode by the investigator.

In the Octaplas® cohort, no AEs were reported. In the OctaplasLG cohort, one serious adverse reaction was reported: severe hypotension in one patient that required treatment with a cardiac stimulant. The patient recovered completely after 20 minutes. Efficacy conclusions could not be drawn because of the observational nature of the study.

Study LAS-203: (Octaplas® G-2a and OctaplasLG in healthy volunteers, IND study, N=60)

The study was designed as an open label, randomized, single center, two-period cross-over study. A cross-over design was chosen to minimize inter-individual variability in the endogenous plasma levels of coagulation factors. Prior to pheresis of 600mL of plasma, each healthy volunteer was randomly assigned to one of two treatment sequences (A or B). Sequence A subjects received OctaplasLG followed by Octaplas®. Sequence B subjects received treatment in the opposite order. The objective of this study was to compare the safety and impact on laboratory parameters of OctaplasLG with Octaplas®. In each case, the volume of Octaplas® or OctaplasLG infused was 1200 mL.

The following parameters were assessed:

- coagulation factors
- hemostatic parameters (aPTT, PT and protein C)
- hematology parameters (RBC count, WBC count, platelets, hematocrit, hemoglobin, PI, and PS),
- clinical chemistry

The primary analysis was to demonstrate equivalence recoveries of coagulation factors using a 10% margin.

For each coagulation parameter the recoveries were analyzed by performing two one-sided paired t-tests of the hypothesis

H_0: |mean(Recovery(OctaplasLG)) - mean(Recovery(Octaplas® SD))| > 10.0

vs.

H_1: |mean(Recovery(OctaplasLG)) - mean(Recovery(Octaplas® SD))| ≤ 10.0.

AEs and vital signs were evaluated for assessment of safety.

A total of 68 healthy subjects were screened for the study, 60 were included in the ITT/Safety population and 43 in the per protocol (PP) population.

All coagulation and hemostatic parameters met the equivalence criterion.

To verify the assumption of improvement of PI concentrations, a test for superiority was conducted. Statistically significant differences between treatments were found at 15 minutes (P=0.0012) and 2 hours (P=0.0190) post-transfusion for the per protocol population. Increased levels of PI post-infusion of OctaplasLG, as compared to Octaplas® may be attributable to the increased levels of PI in the OctaplasLG product.

In total, 158 treatment emergent AEs were reported in 60 subjects (77 in OctaplasLG and 81 in Octaplas®). The AEs (paraesthesia, headache and urticaria) reported in both groups were mild to moderate and there was no imbalance between the two groups.

Section 2: Conclusions

These bridging studies compared OctaplasLG to Octaplas® or UniplasLG. A total of 299 subjects were studied in bridging studies that included 90 healthy volunteers, 84 heart surgery patients, and 125 patients needing plasma for any condition. Comparability was observed in laboratory values, except for PI values in Study LAS-203. Imbalances were not seen in AE rates between treatment groups.

3. Single arm studies

Study 3PLASIV90 (Octaplas® G-1 in patients with hereditary or acquired coagulation factor deficiency, N=11)

In this study the lyophilized form of Octaplas® G-1 was used. The objective of this study was to assess the effects of Octaplas® on coagulation parameters in subjects with a hereditary (FVII, X or XI deficiency, n = 8) or acquired (due to liver disease, n = 3) coagulation factor deficiency.

The study was an open-label, non-controlled, prospective study, conducted in two centers. In total 11 subjects were evaluated. In this study Octaplas® was effective for replacement of deficient coagulation factors as shown by expected recovery levels.

Two patients experienced a total of 3 AEs, consisting of an anaphylactoid reaction, and urticaria with pruritis. These AEs resolved with anti-histamine therapy and both patients recovered. No patient dropped out of the study for safety reasons.

Study LAS-Study 1-D (Octaplas® G-1 in patients in the ICU with coagulopathy, N=30)

The primary objective was to assess the effects of Octaplas® on coagulation and circulation parameters as well as on manifest bleeding in subjects in the ICU with coagulopathy due to blood loss, dilution or DIC.

The study was prospective, open-label, non-controlled, whereby all patients during the postoperative period in the intensive care unit requiring plasma therapy were to be enrolled. In total, 30 subjects were evaluated.

Sixteen of 22 subjects with manifest bleeding demonstrated a hemostatic effect. There were no AEs reported.

Section 4: Safety studies

Study PVI/ 003 and PVI/B004:

PVI/003 and PVI/B004 were very small studies that do not contribute to the overall safety database.

Section 5: Literature reports

As FDA has not had access to the raw data in these reports, it cannot comment on the adequacy of these data to support safety and efficacy.

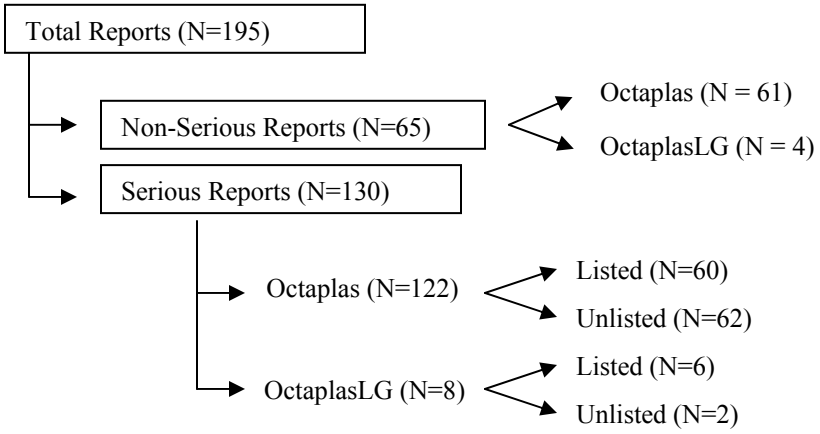
Section 6: Pharmacovigilance [Oct 1989 to Aug 2011]

Octaplas®G-1 and G-2a and OctaplasLG Post-licensure Safety Surveillance Data

- Over 21 years of postmarketing surveillance data are available for Octaplas®G-1 and G-2a. Since the initial Octaplas® approval on 27 October 1989, Octaplas®G-1 and G-2a have been approved in 28 countries worldwide, totaling 7 million units (200mL bags) sold and an estimated 2.3 million patients exposed.
- Over 2 years of postmarketing surveillance data are available for OctaplasLG. Since the first approval in June 2009, OctaplasLG has been approved in 2 countries, totaling 125,000 units (200mL bags) sold and an estimated 41,500 patients exposed.
- From 27 October 1989 to 31 August 2011, a total of 195 adverse event reports for SDP were received worldwide. Of these, 144 (74%) were spontaneous reports

from healthcare providers, 36 (18%) from regulatory authorities, 13 (6%) from the medical literature, and 2 (1%) from clinical studies.

Figure 1: Distribution of 195 Reports between Octaplas and OctaplasLG



** Listed / unlisted refers to whether the adverse event appears in the package label and was determined by Octapharma.*

Serious Reports

Table 6 summarizes all serious reports on a patient basis. Each report was consolidated under the most serious and related condition, in terms of causality, to the administration of one of the generations of Octaplas products as determined by Octapharma pharmacovigilance reviewers. All adverse event reports were represented only once except one case was listed twice as both a suspected transmission and hypersensitivity reaction.

Table 6: Worldwide Summary of Serious Adverse Events for Octaplas®G-1 and G-2a and OctaplasLG — October 1989 to August 2011 (N=130)^

	Report Category	No. Unrelated Cases*		No. Related Cases**	
		Octaplas	OctaplasLG	Octaplas	OctaplasLG
1	Hypersensitivity reactions including anaphylactic and allergic reactions	2	0	42	5
2	Respiratory disorder (not elsewhere classified)	2	0	10	2
3	Circulatory overload	1	0	5	0
4	Seroconversions (passive transfer of antibodies)	0	0	5	0
5	Thromboembolism	0	0	4	0

6	Other (alkalosis, medication error, etc.)	2	0	2	1
7	Cardiac disorder (not elsewhere classified)	4	0	2	0
8	Isolated fever and chills	0	0	2	0
9	Citrate toxicity	0	0	1	0
10	Hyperfibrinolysis	0	0	1	0
11	TRALI	0	0	0	0
12	Hemolytic transfusion reaction	0	0	0	0
13	Suspected transmission of infectious agents	38	0	0	0
	TOTAL	49	0	74	8

* Classified as not related, unlikely, unclassifiable

** Classified as possible or probable

^ All adverse event reports were represented only once except one case was listed twice as both a suspected transmission and hypersensitivity reaction.

The three most frequent serious adverse events reported after Octaplas and OctaplasLG were hypersensitivity reactions, respiratory disorders, and circulatory overload. Reports of thromboembolism and hyperfibrinolysis, historically a source of concern with solvent/detergent-treated plasma products, were also detected.

Table 7: All MedDRA Preferred Terms Associated with the 62 Serious Unlisted Reports for Octaplas/OctaplasLG from Oct 1989-Aug 2011

Category in Table 6 of Clinical Overview	Number of Unrelated Cases	Number of Related Cases
Suspected transmission of infectious agent	38	0
Hypersensitivity reactions including anaphylactic and allergic type of reactions	0	4
Seroconversions (passive transfer of antibodies)	0	5
Cardiac disorder (not elsewhere classified)	4	1
Respiratory disorder (not elsewhere classified)	1	1
Thromboembolism	0	4
Hyperfibrinolysis	0	1
TRALI	1	0

Other (alkalosis, medication error, etc.)	2	1

^ one case was listed twice as both a suspected transmission and hypersensitivity reaction

Table 8 describes all serious reports for OctaplasLG which were received as of 31 August 2011, with 13 serious adverse events (most reports consisted of more than one term).

Table 8: Serious Adverse Events for OctaplasLG Worldwide August 2011

	MedDRA System Organ Class	Preferred Term	No.
1	Immune system disorders	anaphylactic reaction anaphylactoid reaction anaphylactic shock hypersensitivity	1 1 2 –
2	Respiratory disorders	dyspnea lung infiltration respiratory failure	1 1 1
3	Injury, poisoning and procedural complications	allergic transfusion reaction citrate toxicity TRALI	– – 1
4	Nervous system disorders	convulsion	1
5	Metabolism and nutrition disorders	hypervolemia	1
6	Infections and infestations	pneumonia	1
7	General disorders and administration site conditions	malaise	1
8	Investigations	blood pressure decreased	1
		Total	13

** This table lists all adverse events, regardless of causality. Some events, including TRALI, are listed here for completeness but were classified as not-related upon medical review by Octapharma. For categories of events deemed related to OctaplasLG administration, please refer to Table 6.*

Notably, 2 out of 8 reports contained unlisted adverse events, as follows:

Convulsion: A 44-year-old male patient, suffering from a bone marrow transplantation-associated thrombotic thrombocytopenic purpura (TTP), received plasmapheresis treatment with Octaplas LG (S/D treated plasma, 300 mL). During the infusion, the patient experienced severe generalized seizures. Plasmapheresis treatment was interrupted and a neurological examination was performed including a CT scan which did not disclose any findings. The patient completely recovered within 15 min and plasmapheresis treatment was continued a couple of hours later on the same day. The treating physician suspected the seizures to be related to the patient's underlying TTP. Octapharma classified this case as serious, unlisted and possibly related to the administration of Octaplas LG due to the temporal relationship.

Dyspnea, Hypervolemia, possible Transfusion-related acute lung injury, Pneumonia, Lung infiltration, Malaise: A 21-year-old female patient with acute myeloid leukemia. She was treated with platelet concentrates (2 units) and Octaplas LG (2 units). Subsequently, the patient developed dyspnea, malaise and pulmonary infiltrates. The treating physician suspected a pneumonia with the differential diagnosis of TRALI. The hospital tested the platelet concentrate, Octaplas LG and the patient for HNA and HLA antibodies. Octapharma classifies this serious (reported as medically significant) case as unlisted and the symptoms possibly related to the administration of Octaplas LG due to the temporal relationship. The diagnosis of TRALI is considered highly unlikely due to negative HNA and HLA re-tests of the batch. Retests were performed internally, as well as in 2 external laboratories, and all found negative results for the respective antibodies.

Deaths

Reports of deaths occurring in association with the administration of the Octaplas products have been few and most have been judged by the sponsor to be unrelated to the product. Table 8 summarizes those death reports where the fatality was judged by the sponsor to be possibly related to the infusion of the Octaplas product.

Table 9: Summary of Deaths Judged by Octapharma to be Possibly Related to Octaplas®G-1 or G-2a or OctaplasLG

Manufacturer Report Number	Adverse Event (MedDRA preferred term)
LAS-011-02-IRL	fibrinolysis, hemorrhage, coagulopathy
LAS-015-02-IRL	therapeutic response decreased, cardiac arrest, fibrinolysis
LAS-006-07-DE	acute pulmonary edema
LAS-002-06-IRL	hypotension, cardiac arrest
LAS-024-10-LU	pulmonary edema, transfusion related circulatory overload

Postmarket Safety Surveillance Plan Proposed by Octapharma for OctaplasLG in the United States

	Health Outcome	Octapharma Action Plan
Important identified risks	1. Hypersensitivity and anaphylaxis 2. Venous thromboembolism	Routine (passive) surveillance
Important potential risks	3. General virus safety 4. Hemolytic transfusion reaction 5. TRALI 6. Excessive bleeding due to hyperfibrinolysis 7. ABO-incompatible OctaplasLG	Routine (passive) surveillance

	transfusion	
Important missing information	8. Safety in pediatric, elderly and pregnant and nursing women	Routine (passive) surveillance

Summary Discussion

FDA is asking BPAC to consider whether the available data demonstrate that OctaplasLG has an acceptable safety profile and is effective for its proposed indications.

A. Efficacy:

OctaplasLG is a pooled product that adheres to release specifications, thus delivers a standardized volume and concentration of coagulation proteins and inhibitors.

Octapharma submitted data from a number of small studies conducted with different generations of solvent/detergent plasma. These data were submitted in support of the two proposed indications for OctaplasLG:

- Management of preoperative or bleeding patients who require replacement of multiple plasma coagulation factors;

- Substitution of intentionally removed plasma (e.g. plasma exchange in patients with thrombotic thrombocytopenic purpura - TTP);

Three studies were performed comparing Octaplas® to FFP in enrolled subjects: (i) with coagulopathy (n = 67); (ii) undergoing cardiac surgery (n = 66); and (iii) with liver disease and undergoing liver transplantation (n = 52). In all three studies, subjects were divided into active treatment groups receiving either Octaplas® or FFP, and achieved comparable functional levels of coagulation factors, and similar levels of hemostasis (assessed by individual investigators).

The following four bridging studies were performed: (i) Uniplas vs. Octaplas® in cardiac surgery (n =84); (ii) UniplasLG vs. OctaplasLG in healthy volunteers undergoing plasma replacement (n = 30); (iii) Octaplas® vs. OctaplasLG in healthy volunteers undergoing plasma replacement (n = 60): and (iv) Octaplas® vs. OctaplasLG in any clinical condition with a need for plasma (n = 125). In all four studies, subjects were divided into groups receiving either Octaplas® (G-2a) or OctaplasLG. Study subjects achieved comparable functional levels of coagulation factors, and when assessed in bleeding patients, similar levels of hemostasis.

In addition, two single arm studies were performed: (i) Octaplas® in patients with coagulopathy (n = 11); and (ii) Octaplas® in patients with DIC (n = 30). In the former study, functional levels of coagulation factors were recovered. In the latter study, hemostasis was achieved in 16/22 bleeding patients.

B. Safety

In all studies evaluated for safety, reported AEs were mainly mild to moderate and consisted of headache, fever, pruritis and urticaria. One case of severe hypotension requiring therapy was reported and the patient recovered with appropriate management.

In the three studies involving FFP as a comparator, AEs with Octaplas® and FFP were similar in rate and severity. In studies that enrolled subjects with liver disease and liver transplantation (n = 61), unlike a predecessor product (PLAS + S/D) with low PS levels, Octaplas® administration was not associated with thromboembolic events (TE).

One of the major risks of treatment with blood components including plasma is transmission of infectious disease agents. This risk has been largely reduced by donor screening questionnaires, and screening of donors by serology and NAT. OctaplasLG is a product pooled from up to 1520 plasma donations. Risk of patient exposure to a large number of donors is offset by SD treatment to remove enveloped viruses. Risk from non-enveloped viruses in OctaplasLG is reduced by limiting viral load using NAT, and by minimal titer specifications for HAV and B19 neutralizing antibodies. To date, there have been no documented cases of infection with HBV, HCV or HIV associated with the use of Octaplas®.[1] B19 transmission has been reported with the use of SDP manufactured prior to the implementation of Parvovirus B19 DNA limits, i.e., B19 should not exceed more than 10.0 IU/µL in the manufacturing plasma pool. No cases of HAV transmission have been reported.

Octapharma plans to introduce HEV PCR testing for OctaplasLG manufacturing pools beginning November 1, 2012. ----------(b)(4)----------
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Despite the very low presumptive prevalence of vCJD infection in US donors, the pooling of plasma for the manufacture of OctaplasLG may increase the risk of vCJD due t0 the absence of significant prion clearance in manufacturing (i.e. estimated clearance of prion infectivity by the ligand gel column of only 0.83 $\log_{10}$.) Nevertheless, the extensive experience showing reduction in risk of TRALI and related deaths with Octaplas indicates that the demonstrated benefit of TRALI reduction would exceed the potential added vCJD risk.

It should be noted that SD treatment, while useful for viral inactivation/removal, impacts the quality of the product by reducing levels of PI and PS. The manufacturing of OctaplasLG has been modified to reduce this effect so that PI and PS levels are higher than in prior generation Octaplas®. Low levels of PS have been associated with TE events, as discussed below. This concern has been mitigated in the case of OctaplasLG because of higher levels of PS due to modifications in the manufacturing process.

1. Low Protein S levels and risk of Thromboembolism

In 1998, FDA licensed PLAS+SD, a solvent/detergent treated, pooled human plasma, manufactured by V.I. Technologies Inc, Melville, NY. This product is no longer available on the US market. It was associated with TE events especially in liver transplantation and

liver disease. The TE events were believed to be due to low levels of PS in PLAS+SD. Solheim et al.[2] have reported a mean PS level of 64 U/100 mL (range 55-71) in Octaplas® G2a vs. 24 U/100 mL (range 14-37) in PLAS+SD, the normal reference range being 56-168 U/100 mL[3]. Differences in PS between products may be attributable to manufacturing differences. The level of PS in OctaplasLG, the product under discussion by BPAC, is higher than the levels detected in Octaplas®G-2a (Table 3).

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In 2003, Yarranton et al.[4] published a retrospective review of the occurrence of venous thromboembolism (VTE) in 68 consecutive patients with TTP (25 male, 43 female) undergoing plasma exchange (PEX). Eight documented VTE events were noted in seven patients (5 deep venous thromboses (DVTs), 1 pulmonary embolus (PE), 1 PE + pulmonary arterial thrombosis and 1 PE + DVT). VTE occurred at a mean of 53 days following the first PEX. Octaplas® G-2a was the last plasma to be used in PEX prior to the VTE in 7/8 events. Other replacement fluids used were FFP and cryosupernatant (CSP). All the DVTs were associated with central venous catheters. The one pulmonary artery thrombosis was related to a Swan–Ganz catheter in the pulmonary artery. Other acquired precipitating factors for VTE for the eight events included pregnancy (n=1), immobility (n=8), and obesity (n=3).

PS levels were not routinely measured during PEX prior to the VTE event; however, archived plasma samples were available for one patient. Mean PS levels were lower in this patient following Octaplas® compared with CSP; however, for both treatments the mean levels remained within the normal reference range.

Yarranton et al. reported a background rate of 3% for VTE in this patient population[5]. The rate in their study was 12%. There have been no further reports of VTE associated with Octaplas® in the clinical studies, literature references or post-marketing reports.

The risk of TE is still a concern especially where large volumes are needed but this may be mitigated in OctaplasLG which has higher levels of PS (within the lower limit of the reference range, Table 3)

2. Low PI (α_2 antiplasmin) levels and risk of bleeding (hyperfibrinolysis)

Hyperfibrinolysis may occur during orthotopic liver transplantation (OLT) and has been associated with excessive bleeding during the procedure. Low levels of PI in Octaplas® have been implicated in an increased incidence of hyperfibrinolysis seen in patients undergoing OLT, as reported by de Jonge et al.[6] De Jonge and his colleagues reported the experience of 41 patients treated with FFP or Octaplas® (N= 21 FFP, N=20 Octaplas®). Hyperfibrinolysis was seen in 6/21 (29%) of the patients who received FFP and 15/20 (75%) of the patients who received Octaplas®.

Intra-operative plasma samples from both patient groups were analyzed and markers of fibrinolysis (D-Dimer and fibrin degradation products [FDP]) were higher in the Octaplas® group than in the FFP group. This is in contrast to levels at the time of anesthesia onset, when no difference in PI levels was detected between the two groups. PI

levels in the FFP treated group decreased from 0.76 IU/mL to a low of 0.58 IU/mL by procedure end. The PI level in the Octaplas® treated group began at 0.64 IU/mL, dropped to a low of 0.27 IU/mL by the time of reperfusion, and was at a level of 0.40 IU/mL by procedure end. Analysis of the Octaplas® lots used in these patients showed levels of PI to be 0.28 ±0.02 IU/mL (normal, 0.95 – 1.20 IU/mL)[3]. The PI levels in these lots appear to be lower than those measured in OctaplasLG (Table 3).

Two cases of hyperfibrinolysis were reported from Ireland.[7] The authors reported that shortly after the change from FFP to Octaplas® (derived from US donor plasma), 2 of 22 patients died intraoperatively during liver transplantation with severe coagulopathy and excessive bleeding. Both patients were noted to have hyperfibrinolytic activity, indicated by increasing D-Dimer and decreasing fibrinogen. PI levels were not reported.

Solheim et al[8] reported that the Norwegian experience with Octaplas® did not reveal any issues with fibrinolysis during the period of 1993 – 2001, during which 208 liver transplants were performed using Octaplas®.

Since the introduction of OctaplasLG, which has an improved manufacturing process resulting in increased levels of PI, there have been no literature and/or pharmacovigilance reports of an increased incidence of hyperfibrinolysis during liver transplantation.

3. Risk of TRALI

The risk of TRALI is minimized with OctaplasLG because pooling of plasma dilutes neutrophil or HLA antibodies that may be contained in select donor units. No cases of TRALI have been reported in any of the submitted or published clinical studies, nor has any such relevant pharmacovigilance data been submitted to FDA. Current therapy with FFP carries a risk of TRALI ~1:10,000 units, even with male donor only FFP.

Questions to the Committee:

1) Do the data show that OctaplasLG is effective
   i) for the management of preoperative or bleeding patients who require replacement of multiple coagulation factors?
   ii) as substitution of intentionally removed plasma (e.g. plasma exchange in patients with TTP)?

2) Do the data show that OctaplasLG has an acceptable safety profile for the indications stated in question 1?

3) If the answer to question 1 or question 2 is no, what additional studies should be performed premarketing for the proposed indications?

4) Please comment whether safety monitoring would be needed post approval specifically to monitor:

a) thromboembolic events?
b) excessive bleeding?
c) transmission of HEV?

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Appendix 1: Tabulation of Studies reviewed FDA for evaluation of Safety and Efficacy

Study Number Investigator; Site; Study Period; Publication	**Design**	**Number of Subjects**	**Diagnosis/Indication**	**Product Treatment Regimen**	**Evaluation Criteria**	**Results (Efficacy)**	**Results (Safety)**
LAS-1-02-D Haubelt et al; Germany; 1998-1999; ***Vox Sanguinis 2002***	Prospective; Drug surveillance study (cohorts of 5 received FFP or Octaplas® sequentially) Open label	Total n =67; Octaplas® n=36; FFP n=31	Post-op open heart ICU with impaired hemostasis (dilution, blood loss, DIC, or a combination) No formal Inclusion/Exclusion criteria were specified	Octaplas® Generation 2a, dose 600 mL FFP or Octaplas®	Parameters measured before treatment and 60 min after termination of plasma infusion: PT, aPTT, fibrinogen, FVIII, ATIII, free PS and PS activity, prothrombin fragments F1+2, D-dimers, fibrinogen degradation products, plasmin–antiplasmin complexes, plasminogen, PI and trypsin inhibitor	PS activity did not increase after Octaplas® infusion but did show an increase after infusion with FFP. PI declined after Octaplas® and remained uninfluenced by FFP. With the exception of PS and PI, Octaplas® and FFP improved hemostasis and fibrinolysis to a similar degree. Free PS did show improvement with Octaplas® and FFP.	No ADRs reported

Study Number Investigator; Site; Study Period; Publication	**Design**	**Number of Subjects**	**Diagnosis/Indication**	**Product Treatment Regimen**	**Evaluation Criteria**	**Results (Efficacy)**	**Results (Safety)**
19/PLAS/IV/91 Solheim et al; Norway; 1992; ***DIC; Pathogenesis, Diagnosis and Therapy of Disseminated Intravascular Fibrin Formation 1993***	Prospective; Open label (Octaplas® FFP and no plasma groups)	Total n = 66 Octaplas® n=20; no plasma n=26; FFP n=20	Elective open heart surgery	Octaplas® Generation 1, mean dose 700 mL	Blood loss, hematologic and global coagulation parameters	No significant difference in post-op blood loss (Octaplas® vs. FFP), revision for bleeding respirator time, circulatory support and hospital stay (all 3 groups) Octaplas® Group avg 3.5 units (range 1-17), FFP avg 4.05 units (range 2-16)	1 ADR (transient fever reaction in Octaplas® Group)
LAS-1-03-UK Williamson et al; Multi-center UK; 1995-1997; ***Transfusion 1999***	Prospective; Randomized; Open label; Single-blind	Total n = 55 FFP n=25; Octaplas® n=30	LD (PT>4sec) n=24 (FFP n=11, Octaplas® n=13) 23 prior to invasive procedure LT n=28 (FFP n=14, Octaplas® n=14) TTP n=3 (all Octaplas®)	Octaplas® Generation 2a, mean dose 12-13 mL/kg LD, 44 mL/kg LT	Coagulation factors, PTT, INR	Octaplas® and FFP showed similar degrees of correction of prolonged INR and PTT	2 ADRs (nausea, pruritis) reported in 1 subject with LD who received Octaplas®

Study Number Investigator; Site; Study Period; Publication	**Design**	**Number of Subjects**	**Diagnosis/Indication**	**Product Treatment Regimen**	**Evaluation Criteria**	**Results (Efficacy)**	**Results (Safety)**
LAS-203; Jilma; IND 13956 Austria; 2009-2010; ***Publication N/A***	Prospective; Open label; Cross over	60 healthy individuals; PEX after PPh PP n=43	Healthy volunteers	Octaplas® Generation 2a mean dose 1098.1 mL (14.9 mL/kg) and OctaplasLG 1149.5 mL (15.26 mL/kg)	Individual relative recoveries of coagulation Factors I, II, V, VII, VIII, IX, X, XI; hemostatic parameters (aPTT, PT, protein C and PI)	All coagulation and hemostatic parameters met the equivalence criterion	(no premeds) Most freq AEs: HA, paraesthesia, urticaria. 1 SAE of anaphylactic shock with OctaplasLG (withdrawn from study, recovered same day)
UNI-101 Tollofsrud et al; Norway; 1999-2001; ***Intensive Care Med 2003***	Prospective; Randomized; Single-Blinded	Total n = 84 Octaplas® n=19; Uniplas n=36; No plasma n=29	Elective open heart surgery	Uniplas and Octaplas® Generation 2a, dosing according to clinical needs	aPTT, ACT, complement activation, DAT	aPTT and ACT values were comparable in the 3 active treatment groups	AEs were evenly distributed
LAS-201; Multi-center Germany; 2008-2010; ***Publication N/A***	Non-Interventional; Observational	Total n = 125	any	Octaplas® Generation 2a and OctaplasLG	Objective physician assessment based on clinical or lab parameters	Efficacy conclusions could not be drawn because of the observational nature of the study	1 ADR in OctaplasLG subject (severe hypotension)
UNI-110 Jilma; Austria; 2009; ***Publication N/A***	Prospective; Double blind; Cross over	30 healthy individuals; PEX after PPh	Healthy volunteers	OctaplasLG n=29 mean dose 16.2 mL/kg and Uniplas LG n=30 mean dose 16.1 mL/kg	Hemoglobin and other parameters of hemolysis, complement activation, DAT	Mean values of coagulation parameters were within the normal range and variations in their levels were similar between treatment groups	(no premeds) Most freq AEs: HA, paraesthesia, urticaria. No SAEs

Study Number Investigator; Site; Study Period; Publication	**Design**	**Number of Subjects**	**Diagnosis/Indication**	**Product Treatment Regimen**	**Evaluation Criteria**	**Results (Efficacy)**	**Results (Safety)**
3PLASIV90 Inbal et al; Israel; 1990-1992; ***Blood Coagulation and Fibrinolysis 1993***	Prospective; Open label; Single arm	11	Hereditary Factor VII, X, or XI deficiency (n=8); Acquired coagulation disorders due to LD (n=3)	Octaplas® Generation 1, mean dose of 580 mL (range 400 to 1600 mL)	PK parameters, hemostatic efficacy (2 on-going bleeding, 8 prophylaxis prior to invasive procedure, 1 PPh)	In those with hereditary deficiency, the deficient factor showed an increase by calculated recovery, bleeding stopped or no bleeding noted during procedure	3 ADRs in 2 subjects (pruritis and urticaria, anaphylactoid reaction,
LAS-Study 1-D Hellstern et al; Germany; 1992; ***Infusionsther Transfusionmed 1993***	Prospective; Open label; Single arm	30	Post-op admission to ICU and treated for DIC and/or coagulopathy due to blood volume dilution or loss (no formalized in/exclusion criteria)	Octaplas® Generation 1, mean dose 377 mL	Coagulation analysis before and within 10 to 60 min after plasma infusion (PT, fibrinogen, ATIII, aPTT, plts), VS	16/22 subjects with manifest bleeding demonstrated hemostatic effect	No ADRs reported
Study number N/A Chekrizova et al; Multi-center Ireland; 2002-2003; ***Transfusion Medicine 2006***	Retrospective	A. 41 neonates B. 38 adults C. 15 children w/ LD and 17 adults w/ LD	A. Neonates with coagulopathy w or w/o hemorrhage B. OB/Gyn C. LD	Uniplas and Octaplas® Generation 2a A. mean dose 18.4 mL/kg B. mean dose 15.3 mL/kg C. mean dose children 38 mL/kg; adults 10.2 mL/kg	aPTT, PT and fibrinogen	Reported decreases in mean aPTT and PT in neonates, OB/Gyn and LD patients	No ADRs reported

Study Number **Investigator;** **Site;** **Study Period;** **Publication**	**Design**	**Number of Subjects**	**Diagnosis/Indication**	**Product Treatment Regimen**	**Evaluation Criteria**	**Results (Efficacy)**	**Results (Safety)**
Study number N/A Scully et al; Ireland; 2003-2005; ***Vox Sanguinis 2007***	Retrospective	32 subjects (50 acute TTP episodes)	Acute TTP undergoing PEX	Octaplas® Generation 2a and Cryosupernatant		Reported no difference in number of PEX to remission with cryosupernatant and Octaplas®	allergic/ urticarial and citrate reactions were more common with cryosupernatant
Study number N/A Edel et al; Germany; 1998-2006; ***Transfusion Medicine and Hemotherapy 2010***	Retrospective	8	Acute TTP undergoing PEX	Octaplas® Generation 2a, median of mean dose exchanged 43.66 mL/kg	Platelet count, assessment of hemolytic anemia	Reported increase in platelet count to above $150x10^9$/L and disappearance of hemolytic anemia	No ADRs reported
Study number N/A Santagostino et al; multi-center Italy; Period not specified ***The Hematology Journal 2006***	Prospective; Open label; Uncontrolled	17	Inherited coagulation disorders (afibrinogenemia n=1, FV n=4, FV/FVIII n=6, FX n=1, FXI n=5) (14 elective surgery, 2 vaginal delivery, 1 emergent subdural cyst removal)	Octaplas® Generation 2a, median dose 18 mL/kg	PK of deficient factors and hemostatic efficacy	Reported treatment courses judged fully effective (actual blood loss did not exceed expected and no bleeding complications) in 13/16 cases.	1 ADR (rash)
Study number N/A Demeyere et al; Belgium; 2002-2004; ***Vox Sanguinis 2010***	Prospective	40	Semi-urgent cardiac surgery	Octaplas® Generation 2a n=20 PCC n=20	Number of subjects reaching target INR (≤1.5), time to reach target after CPB, post-op bleeding	Reported PCC reversed anticoagulation faster and with less bleeding than Octaplas®	2 ADRs (oozing with Octaplas®)

Adapted from: Octapharma Appendices to Summary of Clinical Safety, Tables 2.7.2.5 February 2011 and 2.7.3.6 November 2011